

## II. REMARKS

### Formal Matters

Claims 7-20, 25-30, and 32-37 are pending after entry of the amendments set forth herein.

Claims 12-16 and 32-37 were examined and were rejected. Claims 7-11, 17-20, and 25-30 were withdrawn from consideration.

The specification is amended as shown above. No new matter is introduced by the amendments to the specification.

Claims 12, 13, 15, and 32-34 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. No new matter is added by these amendments.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

### Objections to the specification

The specification was objected to.

The Office Action stated that at paragraph 00233, “four groups” should be “three groups.”

The Office Action stated that the trademarks in paragraph 00140 should be capitalized and be accompanied by generic terminology.

Applicants respectfully request entry of the above-noted amendments to the specification. Applicants submit that the above-noted amendments to the specification adequately address the objections to the specification.

### Rejection under 35 U.S.C. §112, second paragraph

Claims 12 and 15 were rejected under 35 U.S.C. §112, second paragraph, as allegedly incomplete.

The Office Action stated that the preamble recites a stated goal, and that the claim does not recite a method step to fulfill the stated goal.

Without conceding as to the correctness of this rejection, and solely in the interest of expediting prosecution, claim 12 is amended to recite “wherein an agent that reduces the level of the carboxyl-terminal truncated apoE polypeptide is a candidate agent for modulating a phenomenon associated with

AD”; and claim 15 is amended to recite “wherein a reduction in the formation of detectable product indicates that the agent reduces a proteolytic activity of an enzyme that catalyzes proteolytic degradation of apoE.”

Applicants submit that the rejection of claims 12 and 15 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C. §102(b)

Claims 6-12 and 32-37 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Crutcher and Harmony (WO 98/01101). Claims 6-12 and 32-37 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tolar et al. ((1999) *J. Neurosci.* 19:7100; “Tolar”).

Claims 6-12 and 32-37 over WO 98/01101

The Office Action stated that WO 98/01101 discloses a method of inhibiting the formation of neurotoxic apoE4 fragments in primary chick sympathetic neurons via protease inhibitors; and that WO 98/01101 teaches the use of antipain to prevent the generation of toxic apoE4 fragments. Applicants respectfully traverse the rejection.

WO 98/01101 neither discloses nor suggests a screening method involving identifying agents that reduce formation of a neurotoxic carboxyl-truncated apoE fragment.

WO 98/01101 states: “the present invention is a new method for treating a mammal having a condition associated with toxicity of whole apolipoprotein E or apoE cleavage fragments containing residues 130-169” and states that the method comprises administering a compound that “interferes with production of the toxic fragment or interferes with the receptor-binding site associated with residues 130-169 of the apolipoprotein E molecule.” WO 98/01101, page 6, lines 7-14.

WO 98/01101 focuses on a region of apoE from amino acids 130-169. WO 98/01101 states that the 130-169 region is an apoE receptor binding site, and states that the 130-169 region is contained on whole apoE and on a 22 kD fragment. WO 98/01101, page 7, lines 29-33. WO 98/01101 further states that charged amino acid residues within the 141-149 domain make a significant contribution to apoE

peptide toxicity. WO 98/01101, page 11, lines 30-31. WO 98/01101 states that the 22 kD thrombin cleavage fragment of apoE is neurotoxic, and can be used to assess the efficacy of test compound. WO 98/01101, page 13, lines 30-34. WO 98/01101 discusses an assay to test for inhibition of neurotoxicity of the 22 kD fragment, which assay involves treating neuronal cells *in vitro* with a test agent and 22 kD fragment, and determining the effect of the test agent on inhibition of neurotoxicity of the 22 kD fragment. WO 98/01101, Example 2, page 14, lines 16-31.

However, there is evidence in the instant application that the 22 kD thrombin cleavage fragment of apoE is not neurotoxic. Instead, the instant application provides evidence that carboxyl-terminal truncated apoE fragments that lack amino acids 244-260 are not neurotoxic. Specification, paragraphs 00215 and 00216; and Figure 3B. The 22 kD thrombin cleavage fragment of apoE consists of amino acids 1-191 of apoE. Thus, the 22 kD thrombin cleavage fragment lacks amino acids 244-260 identified in the instant application as essential for neurotoxicity. These data indicate that, in contrast to the assertion in WO 98/01101, the presence of amino acids 130-169 is not critical for neurotoxicity.

In addition, there is evidence in the art that peptides corresponding to the apoE receptor binding site are neuroprotective, not neurotoxic. See, e.g., Aono et al. ((2003) *Neurosci.* 116:437-445; “Aono”; a copy of which is provided herewith). Aono reports that a peptide derived from the receptor binding region of apoE (residues 133-149) completely suppressed neuronal cell death and calcium influx associated with N-methyl-D-aspartate exposure, and that this peptide is thus neuroprotective. Aono, Abstract. Aono discusses the contrast in the observation with the report in Tolar that the 22 kD apoE thrombin cleavage fragment is neurotoxic, states that Tolar used a peptide comprised of tandem repeats of residues 141-149, and showed neuronal cell death upon exposure to this peptide. Aono et al., page 444, column 1, second paragraph. A peptide containing tandem repeats of residues 141-149 is an artificial construct made in the laboratory, and does not exist *in vivo*. Aono further states that the tandem repeat may not be a biologically relevant model of the intact apoE protein. Aono et al., page 444, column 1, second paragraph.

Because WO 98/01101 neither discloses nor suggests a screening method involving identifying agents that reduce formation of a neurotoxic carboxyl-truncated apoE fragment, WO 08/01101 cannot anticipate any of claims 12-16 and 32-37.

Notwithstanding the above remarks, and solely in the interest of expediting prosecution, claim 12 is amended to recite “wherein the neurotoxic carboxyl-terminal truncated apoE polypeptide comprises amino acids 244-260 of apoE.” WO 98/01101 neither discloses nor suggests a screening method involving identifying agents that reduce formation of a neurotoxic carboxyl-truncated apoE fragment, where the neurotoxic carboxyl-terminal truncated apoE fragment comprises amino acids 244-260 of apoE. As such, WO 98/01101 cannot anticipate any of claims 12-16 and 32-37.

Claims 6-12 and 32-37 over Tolar

The Office Action stated that Tolar discloses a method of using a protease inhibitor cocktail to attenuate the production of neurotoxic apoE4 fragments in dissociated chick sympathetic neurons. The Office Action stated that Tolar discloses that protease inhibition reduces the formation of neurotoxic apoE fragments. Applicants respectfully traverse the rejection.

Tolar neither discloses nor suggests a screening method involving identifying agents that reduce formation of a neurotoxic carboxyl-truncated apoE fragment.

Tolar discusses formation of a 22 kD apoE fragment. Tolar, Abstract; page 7102, column 1, first paragraph under “Results.” Tolar states that exposure of neurons to full-length apoE resulted in the appearance of lower molecular weight fragments of apoE, including a 22 kD fragment, “which most likely represents the major N-terminal fragment of apoE.” Tolar, column 1, first paragraph under “Results.” As discussed above, the 22 kD major N-terminal fragment of apoE lacks amino acids 244-260 which were shown in the instant specification to be important for neurotoxicity of carboxyl-terminal truncated apoE. Nowhere does Tolar disclose or suggest inhibition of formation of a neurotoxic carboxyl-terminal truncated apoE fragment.

Because Tolar neither discloses nor suggests a screening method involving identifying agents that reduce formation of a neurotoxic carboxyl-truncated apoE fragment, Tolar cannot anticipate any of claims 12-16 and 32-37.

Notwithstanding the above remarks, and solely in the interest of expediting prosecution, claim 12

is amended to recite “wherein the neurotoxic carboxyl-terminal truncated apoE polypeptide comprises amino acids 244-260 of apoE.” Tolar neither discloses nor suggests a screening method involving identifying agents that reduce formation of a neurotoxic carboxyl-truncated apoE fragment, where the neurotoxic carboxyl-terminal truncated apoE fragment comprises amino acids 244-260 of apoE. As such, Tolar cannot anticipate any of claims 12-16 and 32-37.

Conclusion as to the rejections under 35 U.S.C. §102(b)

Applicants submit that the rejection of claims 6-12 and 32-37 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

### III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GLAD-217CON.

Respectfully submitted,  
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